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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/302,816 03/03/98 ENGELHARDT

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EXAMINER

HM12/0809

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ART UNIT

PAPER NUMBER

1655

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/302,816

Applicant(s)

Engelhardt et al.

Examiner

Arun Chakrabarti

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 30, 2001
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 91-150 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 150 is/are allowed.
- 6) ☒ Claim(s) 91-148 is/are rejected.
- 7) ☒ Claim(s) 149 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) ☐ Other:

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DETAILED ACTION

Priority

1. Applicants are entitled to the priority filing date of the immediate parent application, U.S. Patent Application Serial No. 08/182,621, filed on January 13, 1994.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. Claims 91-96 and 99-120 are rejected under 35 U.S.C. 102 (e) as anticipated by Walker et al (U.S. Patent 5,455,166) (October 3, 1995)

Walker et al teaches an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid, (Abstract, Figures 1 and 2), the process comprising the steps of:

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(a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Example 1, column 10, lines 58-63 and Example 2, column 11, line 63 and Example 3, column 12, lines 49-53);

(b) contacting the sample with a mixture comprising:

(i) nucleic acid precursors (Figure 1)

(ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1 and Example 2, column 11, lines 56-58), and

(iii) an effective amount of a nucleic acid producing catalyst (Example 1, column 11, lines 1-7); and

c) allowing the mixture to react under isostatic conditions of temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figures 1 and 2 and Example 2, column 12, lines 3-6).

Walker teaches the process wherein the nucleic acid is single stranded or double-stranded DNA (Figures 1 and 2 and Examples 1 and 2).

Walker teaches the process wherein the nucleic acid is in solution (Example 2, column 11, line 6 56-62).

Walker teaches the process further comprising the steps of treating the specific nucleic acid with a restriction enzyme capable of producing blunt ends (Figures 1 and 2, column 8, lines 20-60 and example 1, column 11, line 5 and example 2, column 12, line 5).

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Walker teaches the process wherein the nucleic acid is isolated or purified prior to the contacting step or the reacting step (Example 3, column 12, lines 49-52).

Walker teaches the process wherein the releasing step is carried out by means of a restriction enzyme (Figures 1 and 2).

Walker teaches the process wherein the nucleic acid precursors are selected from nucleoside triphosphate and nucleoside triphosphate analogs, or a combination thereof (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the nucleic acid precursors are selected from ATP, GTP, CTP, UTP or TTP (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein the nucleoside triphosphate analogs are naturally occurring or synthetic, or a combination thereof (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein at least one of the nucleoside triphosphate analogs is modified on the phosphate (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the specific nucleic acid primers contains a 3'-hydroxyl group or an isosteric configuration of heteroatoms containing sulfur (Figures 1 and 2 and Example 2, column 11, lines 56-57).

Walker teaches the process wherein the specific nucleic acid primers are not substantially complementary to one another and does not contain more than five complementary to base-pairs in the sequences therein (Column 15, SEQ ID Nos; 5 and 6).

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Walker teaches the process wherein the specific nucleic acid primers comprise from about 5 to 100 nucleotides (SEQ ID Nos: 4-7).

Walker teaches the process wherein the specific nucleic acid primers comprise from about 1 to 200 non complementary nucleotides (Column 15, SEQ ID Nos: 5 and 6).

Walker teaches the process wherein the nucleic acid producing catalyst is selected from DNA polymerase (Example 1, column 11, lines 1-5).

Walker teaches the process further comprising the step of detecting the product by means of incorporating into the product a labeled primer (Example 3, column 12, line 65 to column 13, line 13 and Table III).

Walker teaches the process further comprising the step of regenerating the one or more specific nucleic acid primers for additional production processes (Figures 1 and 2).

4. Claims 142, 144, 146 and 147 are rejected under 35 U.S.C. 102 (b) as anticipated by Zaichikov et al. (Bioorganicheskaya Khimiya, (1988 Jan), Vol. 14 (1), 121-4).

Zaichikov et al teaches a conjugate comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein, and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-3).

Zaichikov et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6).

5. Claims 142-148 are rejected under 35 U.S.C. 102 (b) as anticipated by Knorre et al. (IZV SIB OTD AKAD NAUK SSSR SER BIOL NAUK (1989), Volume 0(2),

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pages 98-104).

Knorre et al. teaches an in vivo process for producing a specific nucleic acid, the process comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein, and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-19).

Knorre et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6) and the nucleic acid construct contains the corresponding RNA polymerase promoter (Abstract, lines 1-8).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 91-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Matthews et al. (Analytical Biochemistry, (1988), Vol. 169, pages 1-25).

Walker teaches the processes of claims 91-96 and 99-120 as described above.

Walker does not teach the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization.

Matthews et al teaches the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization (Figures 9, 10, 12, 13 and 14).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute sandwich hybridization model of Matthews et al. in the method of Walker, since Matthews et al states, "The sandwich hybridization strategy is not limited to quantitation of a nucleic acid species, but can easily be applied to detection of altered restriction sites in DNA, providing the exact mutation to be detected is known (page 16, column 1, lines 7-11)." An ordinary practitioner would have been motivated to combine the sandwich hybridization model of Matthews et al. in the method of Walker, in order to achieve the express advantages noted by Matthews et al. of a method which provides easy application to detection of altered restriction sites in DNA.

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8. Claims 91-96 and 99-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Pardee et al. (U.S. Patent 5,965,409) (October 12, 1999).

Walker teaches the processes of claims 91-96 and 99-120 as described above.

Walker does not teach primers comprising at least one ribonucleic acid segment.

Walker does not teach removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H.

Pardee et al teaches primers comprising at least one ribonucleic acid segment (Column 1, line 66 to Column 2, line 7).

Pardee et al teaches removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H (Column 1, line 66 to Column 2, line 7).

Walker does not teach one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid.

Padree et al. teaches one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid (Column 1, line 66 to Column 2, line 7).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the chemically-modified primers made by RNase H of Pardee et al. in the method of Walker, since Pardee et al state, "This reaction is very efficient (Column 2, lines 5-6)." By employing scientific reasoning, an ordinary practitioner

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would have been motivated to substitute and combine the chemically-modified primers made by RNase H of Pardee et al. in the method of Walker, in order to produce more than a copy of a specific nucleic acid and also in order to achieve the express advantages, as noted by Pardee et al., of a reaction which is very efficient.

9. Claims 91-96, 99-120 and 129-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (U.S. Patent 5,455,166) (October 3, 1995) in view of Pardee et al. (U.S. Patent 5,965,409) (October 12, 1999) further in view of Courey et al. (Journal of Molecular Biology, (1988), Vol. 202, pages 35-43).

Walker in view of Gerdes et al. in view of Pardee et al. teach the processes of claims 91-96, 99-120 and 129-136 as described above.

Walker in view of Pardee et al. do not teach one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed.

Courey et al teaches one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed (Figures 2, 5 and 6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the loop forming supercoiling model of Courey et al. in the

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method of Walker in view of Pardee et al. , since Walker states, "The invention further relates to methods of generating amplified products which can function as probes or templates for sequence analysis (column 4, lines 41-47)." Courey et al provides further motivation as he states, "Lengths of cruciform arms are strongly dependent on sequence imperfections in the palindrome (page 36, column 1, lines 11-14)." An ordinary practitioner would have been motivated to combine the loop forming supercoiling model of Courey et al. in the method of Walker in view of Pardee et al. , in order to achieve the express advantages , as noted by Courey et al., of a method that provides the detection of sequence imperfections in a nucleic acid sample.

Response to Arguments

10. In response to applicant's argument that the Walker reference fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., intermediate structure that is not normally present in the specific target nucleic acid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Zaichikov et al. reference and Knorre et al reference teach the in vitro process only and do not teach the in vivo process. Applicant argues that because Zaichikov et al. reference and Knorre et al have a preferred embodiment of in vitro process only, Zaichikov et al. reference and Knorre et al is limited to the preferred embodiment. As MPEP 2123 states

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“Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 169 USPQ 423 (CCPA 1971).” MPEP 2123 also states “ A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989).” It is clear that simply because Zaichikov et al. reference and Knorre et al have a preferred embodiment , these embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. For example, see page 6, last paragraph of Zaichikov et al and page 14, last paragraph of Knorre et al. Therefore, all 102 rejections have been maintained.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

However, in view of the priority document, 103 (a) rejections in view of Romano et al and Gerdes et al references have been withdrawn and replaced by a new 103 (a) rejection in view of Padree et al.

Allowable Subject Matter

11. No prior art rejection is made against claims 149 and 150.

Conclusion

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

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August 6, 2001



JEFFREY FREDMAN
PRIMARY EXAMINER